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Therapeutic Class Review
Nitrates and Nitrites

I. Overview

The nitrates and nitrites are a class of vasodilating agents primarily indicated for the acute treatment, prophylaxis and management of angina pectoris due to coronary artery disease. Myocardial ischemia develops when there is an imbalance between myocardial oxygen supply and demand which can lead to symptoms such as angina pectoris. Nitrates and nitrites effectively reduce myocardial oxygen demand by increasing blood flow. On the other hand, vasodilation can also lead to side effects, such as headache and flushing. Various formulations are available that differ in both onset and duration of action, which dictates their role in treatment of acute, stable and unstable angina.[1-2]

The nitrates, isosorbide dinitrate in combination with hydralazine in particular, also serve a role in the management of heart failure as an adjunct to standard treatment.[8-10] Furthermore, nitroglycerin administered intravenously is indicated for blood pressure control during cardiovascular procedures while either intravenous or sublingual nitroglycerin is beneficial in the management of patients with acute myocardial infarction.[2]

Frequently repeated or continuous exposure to organic nitrates leads to a decrease in their pharmacological effects. The development of tolerance limits the efficacy of all chronic nitrate therapies regardless of route of administration. Nitrate-free interval dosing can limit the degree of tolerance associated with chronic use.[1]

The nitrates and nitrites that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths.

Table 1. Nitrates and Nitrites Included in this Review

Generic Name	Formulation(s)	Example Brand Name(s)
amyl nitrite	inhalant	N/A*
isosorbide dinitrate	sublingual tablet, sustained-release capsule, sustained-release tablet, tablet	Dilatrate-SR®, Isordil®*
isosorbide mononitrate	sustained-release tablet, tablet	Imdur®*, Ismo®*, Monoket®*
nitroglycerin	injection, ointment, sublingual tablet, sustained-release capsule, transdermal patch, translingual spray	Minitran®*, Nitro-Bid®, Nitro-Dur®*, Nitroglyn®*, Nitrolingual®, Nitrostat®*

*Generic is available in at least one dosage form or strength.

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the nitrates and nitrites are summarized in Table 2.

Table 2. Treatment Guidelines Using the Nitrates and Nitrites

Clinical Guideline	Recommendation(s)
American College of Cardiology/American Heart Association (ACC/AHA) Task Force on	• Use sublingual nitroglycerin (NTG) or NTG spray for immediate relief of angina. • Long-acting calcium-channel blocking agents (CCB) or long-acting nitrates may be used if β-blockers are contraindicated. • Long-acting CCB or long-acting nitrates may be used with β-blockers if initial treatment is

Clinical Guideline	Recommendation(s)
Practice Guidelines: **Guideline Update for the Management of Patients with Chronic Stable Angina (2002)**[3]	not successful. • In 2007 an update to this guidline was published but it did not address the use of the nitrates and nitrites.[4]
American College of Cardiology (ACC)/American Heart Association (AHA): **ACC/AHA 2007 Guidelines for the Management of Patients with Unstable Angina/Non-ST-Elevation Myocardial Infarction (UA/NSTEMI) (2007)**[5]	Clinical Assessment • Patients with suspected acute coronary syndrome should be instructed to take no more than 1 dose of sublingual NTG for chest pain or discomfort. If additional doses are required for persistent or worsening pain, emergency medical attention should be sought. Additional NTG may be taken every 5 minutes for a total of 3 doses while awaiting an ambulance. • Patients with chronic stable angina should be instructed that if symptoms are significantly improved after the first dose of sublingual NTG, doses can be repeated every 5 minutes if needed for a total of 3 doses. If pain does not completely resolve after 3 doses, immediate medical attention should be sought. • Instructions for sublingual NTG administration may be individualized for patients who are known to have frequent angina episodes. The frequency and characteristics of symptoms, as well as the typical response time should be evaluated to determine an appropriate plan. Immediate Management • Low-risk patients that are referred to outpatient stress testing should be given medications such as sublingual NTG, aspirin and/or β-blockers as a preventative measure prior to receiving test results. Anti-Ischemic Therapy • Sublingual NTG (0.4 mg) should be given to patients with UA/NSTEMI and continuing angina every 5 minutes as needed for up to 3 doses. An evaluation of the need for intravenous (IV) NTG, if not contraindicated, should then be performed. • An evaluation as to whether to administer IV NTG should be performed after alternative mortality-reducing interventions with agents such as β-blockers or angiotensin-converting enzyme inhibitors (ACEI) have been utilized. • IV NTG is indicated during the first 48 hours after UA/NSTEMI and continuing ischemia, heart failure (HF) or hypertension. • The recommended starting dose of IV NTG is 10 µg/min and then titrated by 10 µg/min every 3-5 minutes until patient is either nonsymptomatic or a response in blood pressure is seen. • Once the dose has reached 20 µg/min and no response has been noted, an increase of 10 µg/min and then 20 µg/min may be used. • In the absence of relief of symptoms, the goal is to achieve a response in blood pressure. Once this is reached, the dose of IV NTG should then be decreased and the dosing intervals should be extended. • The maximum dose of IV NTG has not been established although it is generally considered to be 200 µg/min. • Topically or orally administered nitrates are considered options for patients without persistent refractory ischemic symptoms but who require additional treatment for angina. • Once patients have been symptom-free for 12-24 hours IV NTG doses should be decreased and converted to oral or topical nitrates. • Nitrates should not be given under the following circumstances: in patients with UA/NSTEMI with systolic blood pressure <90 mm HG or ≥30 mm Hg below baseline, in cases of severe bradycardia [<50 beats per minute (bpm)], in patients with tachycardia (>100 bpm) in nonsymptomatic HF or right ventricular infarction. • Nitrates are also contraindicated within 24 hours of receiving sildenafil or 48 hours of taking tadalafil. The appropriate time between vardenafil utilization and nitrate

Clinical Guideline	Recommendation(s)
	administration has not been established. • Nitrate-free intervals are recommended in patients on oral or topical nitrates and decreases in IV doses should be attempted whenever possible to avoid tolerance. Post-UA/NSTEMI • All patients post-UA/NSTEMI should be given sublingual or spray NTG. • Sublingual NTG should be used for anginal discomfort that has not been relieved by discontinuation of activity or removal from a stressful event. If symptoms persist or worsen after 5 minutes emergency medical services should be contacted. Doses can be repeated every 5 minutes if needed for 3 total doses while patient is lying down or sitting. Long-Term Medical Therapy and Secondary Prevention • NTG is recommended to treat ischemic symptoms.
American College of Cardiology (ACC)/American Heart Association (AHA): **Guidelines for the Management of Patients with ST-Elevation Myocardial Infarction (STEMI)– Pharmacological Management (2004)[6]**	Initial Emergency Department Management • Sublingual NTG 0.4 mg should be given to patients with ongoing ischemic discomfort every 5 minutes for 3 total doses. After 3 doses, assess need for IV NTG. • IV NTG is indicated for relief of ongoing ischemic discomfort, control of hypertension or management of pulmonary congestion. Hospital Management–Medication Assessment • IV NTG is indicated during the first 48 hours for treatment of persistent ischemia, hypertension or congestive heart failure (CHF), provided that therapy does not preclude treatment with β-blockers or ACEI. • NTG after 48 hours can be useful for recurrent angina or persistent CHF provided that therapy does not preclude treatment with β-blockers or ACEI. • In 2007 an update to this guidline was published but it did not address the use of the nitrates and nitrites.[7]
American College of Physicians: **Primary Care Management of Chronic Stable Angina and Asymptomatic Suspected or Known Coronary Artery Disease (2004)[8]**	• Sublingual NTG or NTG spray should be given for immediate angina symptomatic relief. • Long-acting nitrates or long-acting CCBs may be used for symptomatic chronic stable angina if β-blockers are contraindicated. • Long-acting nitrates or long-acting CCBs may be used with β-blockers if monotherapy is not successful in treating symptomatic chronic stable angina. • Nitrates have not demonstrated any reduction in mortality in either post-myocardial infarction (MI) patients or in patients with coronary artery disease (CAD).
European Society of Cardiology (ESC): **Management of Stable Angina Pectoris (2006)[9]**	• Short-acting NTG may be used for prompt relief or prevention of angina, and should be offered to all patients with stable angina. • Long-acting nitrates or CCBs may be considered if β-blockers are contraindicated or inadequately controlling symptoms. A nitrate-free regimen should be implemented to avoid tolerance. • If CCBs alone or in combination with β-blockers, do not adequately relieve symptoms, long-acting nitrates should be considered. • Continuous transdermal NTG therapy is ineffective and it is recommended that patches be removed for a portion of the day. • Long-acting nitrates have shown no clinical benefit over either β-blockers or CCBs.
European Society of Cardiology (ESC): **Guidelines for the Diagnosis and Treatment of Non-ST-Segment Elevation Acute Coronary Syndromes**	• IV nitrates may be considered in patients with non-ST-segment elevation acute coronary syndrome (NSTE-ACS) who require hospitalization. Once symptoms are controlled, a non-parenteral alternative should be used at intermittent dosing intervals to avoid tolerance. • Nitrates administered IV or orally are effective in treating acute symptoms of angina. • Patients with NSTE-ACS should be initiated on sublingual or IV NTG with caution given to those with systolic blood pressure <90 mm Hg.

Clinical Guideline	Recommendation(s)
(2007)[10]	
European Society of Cardiology (ESC): **Management of Acute Myocardial Infarction in Patients Presenting with ST-segment Elevation (2003)[11]**	Recommended Routine Prophylactic Therapies in the Acute Phase • Routine use of nitrates in the initial phase of MI has not shown to be of convincing value and is not recommended. Secondary Prevention • Nitrates should be used only in the presence of angina pectoris.
National Institute for Health and Clinical Excellence (NICE): **Myocardial Infarction: Secondary Prevention in Primary and Secondary Care for Patients Following a Myocardial Infarction (2007)[12]**	Patients With Prior Myocardial Infarction Without Heart Failure • CCBs, nitrates, and potassium channel activators (not currently available in the U.S.) have no effect on premature mortality and can be used for management of risk factors such as hypertension in patients intolerant to a β-blocker and an ACEI.
American College of Cardiology (ACC)/American Heart Association (AHA) Task Force for Practice Guidlines: **Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult (2005)[13]**	• The addition of a combination of hydralazine and a nitrate is reasonable for patients with HF who are already taking an ACEI and β-blocker for symptomatic HF, but who have persistent symptoms. • A combination of hydralazine and a nitrate might be reasonable in patients with current or prior symptoms of HF and reduced left ventricular ejection fraction (LVEF) who cannot be given an ACEI or an angiotensin II receptor blocker (ARB) because of drug intolerance, hypotension, or renal insufficiency. • Combination of hydralazine and isosorbide dinitrate is recommended as part of standard therapy in addition to β-blockers and ACEI for African Americans with New York Heart Association (NYHA) functional class III or IV HF. Any potential benefit in other patients has yet to be evaluated. • Patients with HF should be given nitrates and β-blockers for the treatment of angina.
Heart Failure Society of America (HFSA): **Comprehensive Heart Failure Practice Guidelines (2006) [14]**	• Combination of hydralazine and isosorbide dinitrate is recommended as part of standard therapy in addition to β-blockers and ACEI for African Americans with left ventricular systolic dysfunction. • May be considered in non–African American patients with left ventricular dysfunction (LVD) who remain symptomatic despite optimized standard therapy and in patients who do not tolerate ARB therapy.
European Society of Cardiology (ESC): **Guideline for the Diagnosis and Treatment of Chronic Heart Failure (2005)[15]**	• Patients should be counseled on the possible role of nitrates in sublingual or spray formulation as they may be used as temporary treatment at the onset, or in some cases prophylactically, for dyspnea. • Nitrates may be used as adjunctive therapy for angina or relief of dyspnea. • Nitrates in combination with hydralazine may be considered for the management of HF in cases of intolerance to ACEI and ARBs. Caution should be used because of the risk of developing hypotension. • The addition of long-acting nitrates is recommended in patients with symptomatic systolic LVD and comorbid angina or hypertension.
European Society of Cardiology (ESC): **Guideline on the Diagnosis and Treatment of Acute Heart Failure (2005)[16]**	• In most patients with acute HF as first line therapy, if hypoperfusion is associated with and adequate blood pressure and signs of congestion with low diuresis, to open the peripheral circulation and to lower pre-load; vasodilators are indicated. • In acute MI nitrates may be given orally, however IV formulations are also well tolerated.
National Institute for Health and Clinical	• An isosorbide/hydralizine combination may be used in patients with HF who are intolerant to ACEI or ARB's.

Clinical Guideline	Recommendation(s)
Excellence (NICE): **Management of Chronic Heart Failure in Adults in Primary and Secondary Care (2003)**[17]	
Joint National Committee (JNC): **The Seventh Report Of The Joint National Committee On Prevention, Detection, Evaluation, And Treatment Of High Blood Pressure (2003)**[18]	• IV NTG, at a rate of 5-100 µg/min, is among the treatment options for the management of hypertensive emergencies, particularly in the setting of coronary ischemia. Intravenous NTG's onset and duration of action are 2-5 minutes and 5-10 minutes, respectively.

III. Indications

FDA-approved indications for the nitrates and nitrites are noted in Table 3. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided are based exclusively upon the results of such clinical trials.

Table 3. FDA-Approved Indications for the Nitrates and Nitrites [19-31]

Indication	Amyl Nitrite	Isosorbide Dinitrate*†	Isosorbide Mono-nitrate†	Nitroglycerin		
				Sublingual Tablet/Spray	Injection	Capsule SR, Trans-dermal†
Acute angina pectoris due to coronary artery disease	✔			✔		
Acute prophylaxis of angina pectoris due to coronary artery disease				✔		
Control of congestive heart failure in the setting of acute myocardial infarction					✔	
Induction of intraoperative hypotension					✔	
Prevention of angina pectoris due to coronary artery disease		✔	✔			✔
Treatment of angina pectoris due to coronary artery disease		✔	✔ ‡			
Treatment of angina pectoris in patients who have not responded to sublingual nitroglycerin and β-blockers					✔	
Treatment of perioperative hypertension					✔	

*Because the onset of action of sublingual isosorbide dinitrate is significantly slower than that of sublingual nitroglycerin, sublingual isosorbide dinitrate is not the drug of first choice for aborting an acute anginal episode.
†The onset of action of oral isosorbide dinitrate (immediate or sustained-release), oral isosorbide mononitrate, oral nitroglycerin capsules, or transdermal nitroglycerin is not sufficiently rapid for these products to be useful in aborting an acute anginal episode.
‡Monoket and equivalents

IV. Pharmacokinetics

The pharmacokinetic parameters for the nitrates and nitrites are summarized in Table 4.

Table 4. Pharmacokinetic Parameters of the Nitrates and Nitrites[19-35]

Drug	Bioavailability (%)	Onset (minutes)	Duration	Active Metabolites	Half-Life
Amyl nitrite	Not reported	0.5	3-15 min	Not reported	Not reported
Isosorbide dinitrate sublingual tablet	40-50	2-10	1-2 hours	2-mononitrate, 5-mononitrate	1-4 hours
Isosorbide dinitrate sustained-release capsule/tablet	Not reported	60	Up to 8 hours	2-mononitrate, 5-mononitrate	1-4 hours
Isosorbide dinitrate tablet	10-90	45-60	4-6 hours	2-mononitrate, 5-mononitrate	1-4 hours
Isosorbide mononitrate sustained–release tablet	100	30-60	12 hours	None	4 hours
Isosorbide mononitrate tablet	100	30-60	12 hours	None	4 hours
Nitroglycerin injection	Not reported	Immediate	3-5 minutes	1,2- dinitroglycerols, 1,3-dinitroglycerols	1-4 minutes
Nitroglycerin ointment	Not reported	15-60	2-12 hours	1,2- dinitroglycerols, 1,3-dinitroglycerols	1-4 minutes
Nitroglycerin sublingual tablet	40	1-3	30-60 min	1,2- dinitroglycerols, 1,3-dinitroglycerols	1-4 minutes
Nitroglycerin sustained-release capsule	Not reported	20-45	4-8 hours	1,2- dinitroglycerols, 1,3-dinitroglycerols	1-4 minutes
Nitroglycerin transdermal patch	Not reported	40-60	18-24 hours	1,2- dinitroglycerols, 1,3-dinitroglycerols	1-4 minutes
Nitroglycerin translingual spray	Not reported	2	30-60 minutes	1,2- dinitroglycerols, 1,3-dinitroglycerols	1-4 minutes

V. Drug Interactions

Significant drug interactions with the nitrates and nitrites are listed in Table 5.

Table 5. Significant Drug-Drug Interactions with the Nitrates and Nitrites[36]

Drug(s)	Significance Level	Interaction	Mechanism
Nitrates and nitrites	1	Sildenafil, tadalafil, vardenafil	Sildenafil may potentiate the hypotensive effects of nitrates. The use of these agents in combination is contraindicated.
Nitrates and nitrites	2	Dihydro-ergotamine	The metabolism of dihydroergotamine is decreased thus increasing its bioavailability. The dose of the dihydroergotamine may need to be decreased.

Significance Level 1=major severity
Significance Level 2=moderate severity

VI. Adverse Drug Events

The most common adverse reactions reported with the nitrates and nitrites are noted in Table 6.

Table 6. Adverse Drug Events (%) Reported with the Nitrates and Nitrites[19-31]

Adverse Event(s)	Amyl Nitrite	Isosorbide Dinitrate	Isosorbide Mononitrate SR	Isosorbide Mononitrate	Nitroglycerin
Cardiovascular					
Abnormal heart sound	-	-	≤5	-	-
Aggravated angina pectoris	-	-	≤5	-	-
Angina pectoris	-	-	-	<1	-
Arrhythmia	-	-	≤5	<1	-
Atrial fibrillation	-	-	≤5	<1	-
Bradycardia	-	-	≤5	-	-
Bundle branch block	-	-	≤5	-	-
Cardiac failure	-	-	≤5	-	-
Crescendo angina	-	✔	-	-	✔
Extrasystole	-	-	≤5	-	-
Flushing	✔	-	≤5	-	✔
Heart murmur	-	-	≤5	-	-
Hypertension	-	-	≤5	-	-
Hypotension	✔	✔	≤5	<1	✔
Migraine	-	-	≤5	-	-
Myocardial infarction	-	-	≤5	-	-
Palpitation	-	-	≤5	<1	✔
Postural hypotension	-	-	-	<1	✔
Premature ventricular contraction	-	-	-	<1	-
Q wave abnormality	-	-	≤5	-	-
Rebound hypertension	-	✔	-	-	✔
Supraventricular tachycardia	-	-	-	<1	-
Syncope	✔	✔	✔	<1	✔
Tachyarrhythmia	✔	-	-	-	-
Tachycardia	-	-	≤5	-	-
Ventricular tachycardia	-	-	≤5	-	-
Central Nervous System					
Anxiety	-	-	≤5	<1	-
Confusion	-	-	≤5	<1	-
Decreased libido	-	-	≤5	-	-
Depression	-	-	≤5	-	-
Dizziness	-	✔	8-11	3-5	✔
Headache	✔	✔	38-57	19-38	✔
Impotence	-	-	≤5	<1	-
Insomnia	-	-	≤5	<1	-
Lightheadedness	✔	-	-	-	✔
Nervousness	-	-	≤5	<1	-
Neuritis	-	-	≤5	-	-
Paresis	-	-	≤5	-	-
Paresthesia	-	-	≤5	-	-
Purpura	-	-	≤5	-	-
Somnolence	-	-	≤5	-	-
Vertigo	-	-	≤5	-	✔
Dermatological					
Acne	-	-	≤5	-	-
Anaphylactoid reactions	-	-	-	-	✔

Adverse Event(s)	Amyl Nitrite	Isosorbide Dinitrate	Isosorbide Mononitrate SR	Isosorbide Mononitrate	Nitroglycerin
Contact dermatitis	-	-	-	-	✔ *
Exfoliative dermatitis	-	-	-	-	✔
Photophobia	-	-	≤5	-	-
Pruritus	-	-	≤5	<1	-
Rash	✔	-	≤5	<1	✔
Skin nodule	-	-	≤5	-	-
Endocrine and Metabolic					
Edema	-	-	≤5	<1	-
Gastrointestinal					
Abdominal pain	-	-	≤5	<1	-
Constipation	-	-	≤5	-	-
Diarrhea	-	-	≤5	<1	-
Dyspepsia	-	-	≤5	<1	-
Flatulence	-	-	≤5	-	-
Gastric ulcer	-	-	≤5	-	-
Gastritis	-	-	≤5	-	-
Hemorrhagic gastric ulcer	-	-	≤5	-	-
Loose stools	-	-	≤5	-	-
Nausea	✔	-	≤5	2-4	✔
Vomiting	✔	-	≤5	2-4	✔
Genitourinary					
Dysuria	-	-	-	<1	-
Polyuria	-	-	≤5	-	-
Renal calculus	-	-	≤5	-	-
Urinary tract infection	-	-	≤5	-	-
Hematologic					
Hemolytic anemia	✔	-	-	-	-
Hypochromic anemia	-	-	≤5	-	-
Methemoglobulinemia	✔	✔	✔	✔	✔
Thrombocytopenia	-	-	≤5	-	-
Laboratory Test Abnormalities					
Elevated SGOT	-	-	≤5	-	-
Elevated SGPT	-	-	≤5	-	-
Musculoskeletal					
Arthralgia	-	-	≤5	<1	-
Asthenia	✔	-	≤5	<1	-
Muscle weakness	-	-	≤5	-	-
Musculoskeletal pain	-	-	≤5	-	-
Myalgia	-	-	≤5	-	-
Respiratory					
Bronchitis	-	-	≤5	<1	-
Bronchospasm	-	-	≤5	-	-
Coughing	-	-	≤5	-	-
Dyspnea	✔	-	≤5	-	-
Increased sputum	-	-	≤5	-	-
Nasal congestion	-	-	≤5	-	-
Pharyngitis	-	-	≤5	-	-
Pneumonia	-	-	≤5	<1	-
Pulmonary infiltration	-	-	≤5	-	-

Adverse Event(s)	Amyl Nitrite	Isosorbide Dinitrate	Isosorbide Mononitrate SR	Isosorbide Mononitrate	Nitroglycerin
Rales	-	-	≤5	-	-
Rhinitis	-	-	≤5	-	-
Sinusitis	-	-	≤5	-	-
Upper-respiratory tract infection	-	-	-	<1	-
Other					
Abnormal hair texture	-	-	≤5	-	-
Abnormal vision	-	-	≤5	-	-
Agitation	-	-	-	<1	-
Atrophic vaginitis	-	-	≤5	-	-
Back pain	-	-	≤5	-	-
Bacterial infection	-	-	≤5	-	-
Blurred vision	-	-	-	<1	-
Breast pain	-	-	≤5	-	-
Chest pain	-	-	≤5	-	-
Cold sweat	-	-	-	<1	-
Collapse	-	-	-	-	✔
Conjunctivitis	-	-	≤5	-	-
Diplopia	-	-	-	<1	-
Dry mouth	-	-	≤5	-	-
Dyscoordination	-	-	-	<1	-
Earache	-	-	≤5	-	-
Fatigue	-	-	≤5	-	-
Fever	-	-	≤5	-	-
Flu-like symptoms	-	-	≤5	-	-
Frozen shoulder	-	-	≤5	-	-
Glossitis	-	-	≤5	-	-
Hemorrhoids	-	-	≤5	-	-
Hot flashes	-	-	≤5	-	-
Hyperuricemia	-	-	≤5	-	-
Hypoesthesia	-	-	≤5	<1	-
Hypokalemia	-	-	≤5	-	-
Hypokinesia	-	-	-	<1	-
Impaired concentration	-	-	≤5	-	-
Increased appetite	-	-	-	<1	-
Increased sweating	-	-	≤5	-	-
Intermittent claudication	-	-	≤5	-	-
Leg ulcer	-	-	≤5	-	-
Malaise	-	-	≤5	<1	-
Melena	-	-	≤5	-	-
Moniliasis	-	-	≤5	-	-
Myositis	-	-	≤5	-	-
Nightmares	-	-	-	<1	-
Pallor	-	-	-	-	✔
Paroniria	-	-	≤5	-	-
Ptosis	-	-	≤5	-	-
Restlessness	✔	-	-	-	✔
Rigors	-	-	≤5	<1	-
Tendon disorder	-	-	≤5	-	-
Tenesmus	-	-	-	<1	-

Adverse Event(s)	Amyl Nitrite	Isosorbide Dinitrate	Isosorbide Mononitrate SR	Isosorbide Mononitrate	Nitroglycerin
Tinnitus	-	-	≤5	-	-
Tooth disorder	-	-	-	<1	-
Tremor	-	-	≤5	-	-
Tympanic membrane perforation	-	-	≤5	-	-
Varicose veins	-	-	≤5	-	-
Viral infection	-	-	≤5	-	-
Weakness	-	-	-	-	✔

SGOT=serum glutamic-oxaloacetic transaminase, SGPT=serum glutamic-pyruvic transaminase, SR=sustained-release
*Topical formulations only
✔ Percent not specified
- Event not reported or incidence <1%

VII. Dosing and Administration

The usual dosing regimens for the nitrates and nitrites are summarized in Table 7.

Table 7. Usual Dosing for the Nitrates and Nitrites[19-31, 35]

Drug(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Amyl nitrite	Inhalant: 2-6 inhalations holding capsule under nose, repeat in 3-5 minutes as needed	Safety and efficacy in children have not been established.	Inhalant
Isosorbide dinitrate sublingual tablet	Sublingual tablet: 2.5-5 mg 15 minutes prior to activity	Safety and efficacy in children have not been established.	Sublingual tablet: 2.5 mg 5 mg
Isosorbide dinitrate sustained-release capsule/tablet	Sustained-release capsule/tablet: 40 mg every 8-12 hours; maximum: 160 mg daily	Safety and efficacy in children have not been established.	Sustained-release capsule: 40 mg Sustained-release tablet: 40 mg
Isosorbide dinitrate tablet	Tablet: initial, 5-20 mg 2-3 times daily; maintenance, 10-40 mg 2-3 times daily; A daily dose-free interval of at least 14 hours is advisable to minimize tolerance	Safety and efficacy in children have not been established.	Tablet: 5 mg 10 mg 20 mg 30 mg 40 mg
Isosorbide mononitrate sustained-release tablet	Sustained-release tablet: initial, 30-60 mg once daily may increase to 120 mg once daily; Rarely, 240 mg once daily may be required	Safety and efficacy in children have not been established.	Sustained-release tablet: 30 mg 60 mg 120 mg
Isosorbide mononitrate tablet	Tablet: 20 mg twice daily given 7 hours apart	Safety and efficacy in children have not been established.	Tablet: 10 mg 20 mg
Nitroglycerin injection	Injection: 5 µg/min, increase by 5 µg/min every 3-5 minutes to 20 µg/min. If no response at 20 µg/min increase by 10 µg/min every 3-5 minutes, up to 200 µg/min	Safety and efficacy in children have not been established.	Vial: 0.1 mg/mL 0.2 mg/mL 0.4 mg/mL 5 mg/mL
Nitroglycerin	Ointment: initial, 1/2 inch (7.5 mg) twice	Safety and efficacy in	Ointment:

Drug(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
ointment	daily, 2nd dose applied 6 hours later; dose may be doubled then doubled again	children have not been established.	2%
Nitroglycerin sublingual tablet	Acute relief of anginal attack Sublingual tablet: One tablet dissolved under tongue or in the buccal pouch at the first sign of an acute angina attack, may repeat every 5 minutes up to 3 doses in a 15-minute period Prophylaxis of an angina attack Sublingual tablet: One tablet 5-10 minutes prior to activity	Safety and efficacy in children have not been established.	Sublingual tablet: 0.3 mg 0.4 mg 0.6 mg
Nitroglycerin sustained-release capsule	Sustained-release capsule: 2.5-6.5 mg 3-4 times daily	Safety and efficacy in children have not been established.	Sustained-release capsule: 2.5 mg 6.5 mg 9 mg
Nitroglycerin transdermal patch	Transdermal patch: initial, 0.2-0.4 mg/hour up to 0.8 mg/hour with a patch-off period of 10-12 hours	Safety and efficacy in children have not been established.	Transdermal patch: 0.1 mg/hr 0.2 mg/hr 0.3 mg/hr 0.4 mg/hr 0.6 mg/hr 0.8 mg/hr
Nitroglycerin translingual spray	Translingual spray: 1-2 sprays onto or under tongue no more than 3 sprays in a 15-minute period, 5-10 minutes prior to activity	Safety and efficacy in children have not been established.	Translingual spray: 400 µg

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the nitrates and nitrites are summarized in Table 8.

Table 8. Comparative Clinical Trials Using the Nitrates and Nitrites

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Stable Angina				
Parker et al[37] ISMN 5 mg BID vs ISMN 10 mg BID vs ISMN 20 mg BID vs placebo	DB, PC, PG Patients with stable angina	N=214 3 weeks	Primary: Total exercise duration and time to moderate angina Secondary: Not reported	Primary: Patients underwent testing prior to exercise as well as 2 and 7 hours after each dose on days 1 and 14. Additionally, on days 7 and 21, testing was performed 2 hours after the first dose. ISMN, at all doses, showed improvement over placebo at 2 and 7 hours after the morning dose and 2 hours after the second dose on day 1. Active treatment prolonged exercise duration over placebo at 2 hours postdose for each of the 2 daily doses. ISMN 20 mg was the only strength which demonstrated increased exercise duration 7 hours after administration, which occurred on day 14. Overall, there were fewer episodes of angina noted in the ISMN 20 mg group (*P* values not reported). Secondary: Not reported
Thadani et al[38] ISMN 20 mg BID vs placebo Patients were allowed to continue β-blocker therapy.	DB, MC, PC, PG, RCT Patients with stable exertional angina who stopped treadmill exercise secondary to angina pectoris	N=116 2 weeks	Primary: Total exercise duration (time to moderately severe angina) Secondary: Magnitude of ST-segment depression, heart rate, systolic and diastolic blood pressure, number of anginal	Primary: A statistically significant improvement in total exercise duration was observed at both the morning and afternoon dose compared to placebo ($P<0.01$). Secondary: The magnitude of ST-segment depression was comparable in both the isosorbide-5-mononitrate and placebo groups (1.2±0.1 mm vs 1.2±0.2 mm; $P>0.2$). Heart rate and systolic blood pressure, during the period of exercise, was determined to be similar among the groups. Additionally, the number of anginal attacks and doses of nitroglycerin were no different per group.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			attacks, number of nitroglycerin doses	
Chrysant et al[39] ISMN ER 30 mg QAM vs ISMN ER 60 mg QAM vs ISMN ER 120 mg QAM vs ISMN ER 240 mg QAM vs placebo	DB, RCT Patients with stable effort-induced angina	N=313 6 weeks	Primary: Mean change from baseline in total exercise time (serial exercise testing immediately prior to and 4 and 2 hours after administration, on days 1, 7, 14, 28 and 42) Secondary: Adverse effect	Primary: A significant improvement in mean total exercise time of 30 to 50 seconds was shown in all active-treatment groups compared to placebo at 4 and 12 hours postdose ($P<0.01$). The mean changes from baseline in total exercise time in patients on ISMN ER 120 mg or 240 mg surpassed placebo by about 50 to 60 seconds at 4 hours postdose ($P<0.01$), and by 30 to 35 seconds 12 hours after dosing ($P\leq0.05$). There was no meaningful difference in response found between active treatment and placebo at 24 hours after administration, thus no indication that ISMN ER induced rebound angina. Secondary: The most common adverse effect among active treatment groups was transient headache.
Bray et al[40] NTG administered buccally vs NTG administered sublingually	DB, MC Patients with proven chronic stable exercise-induced angina	N=Not reported Duration not reported	Primary: Efficacy Secondary: Not reported	Primary: The two formulations had comparable effects on acute attacks of angina pectoris. Secondary: Not reported
Ryden et al[41] NTG administered buccally	MC, XO Patients with stable angina	N=126 2 weeks	Primary: Efficacy Secondary:	Primary: Buccal nitroglycerin resulted in 31% less acute anginal attacks compared to the sublingual formulation ($P<0.001$). Prophylaxis was effective in 74% of patients taking buccal NTG compared to 66% of sublingual-treated patients ($P<0.05$).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs NTG administered sublingually	pectoris		Ease of use, patient preference	Secondary: There was no difference in ease of use reported in 67% of patients, whereas 19% indicated that sublingual NTG was easier and 14% buccal NTG. Overall, 65% of patients preferred buccal NTG and 19% preferred sublingual NTG (P<0.05). As far as prophylactic use, buccal administration was again preferred by more patients (81%) than sublingual use (4%; P<0.05).
Demots et al[42] NTG 0.2 mg/hour or 0.4 mg/hour TD for 12 hours (Group A) vs NTG 0.6 mg/hour or 0.8mg/hour TD for 12 hours (Group B) vs placebo The concurrent use of β-blockers was greater in Group A.	DB, RCT Patients with chronic stable angina	N=206 4 weeks	Primary: Effectiveness in chronic stable angina (serial treadmill testing performed 0, 4, 8 and 12 hours after patch application at baseline and on days 1, 15 and 29) Secondary: Adverse reaction	Primary: Improved walking times were observed in both Group A and Group B over placebo at all testing points after short-term administration. Results were statistically significant for Group A at 12 hours and for Group B at 4, 8 and 12 hours (P values not reported). At weeks 2 and 4, walking times were again greater in Group B over placebo at all testing points with the 4 hour test time at week 2 and the 8 hour test time at week 2 and 4 reaching statistical significance (P values not reported). Group A did not demonstrate increased duration in walking time long-term. Secondary: Active therapy was generally tolerated well. An increase in nonexertional angina during the patch-off interval was reported in 9 patients.
Unstable Angina				
Dellborg et al[43] NTG IV for 24 hours vs	RCT Patients admitted to the coronary care unit due to unstable angina	N=29 24 hours	Primary: Efficacy Secondary: Adverse effects	Primary: Efficacy was comparable in the two groups Secondary: Less adverse effects (headache, hemodynamic intolerance) were associated with buccal nitroglycerin than IV although the differences were not significant.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
NTG administered buccally every 4 hours				
Kaplan et al[44] NTG IV 10 µg/min increased by 10 µg/min every 5 minutes to 50 µg/min then increased by 50 µg/min per each episode of angina	OL, OS Patients with angina at rest unresponsive to standard therapy including oral or topical nitrates and β-blockers	N=35 24 hours	Primary: Clinical response Secondary: Not reported	Primary: NTG therapy reduced the number of episodes of angina at rest from 3.5±0.4 to 0.3±0.1, reduced doses of sublingual NTG from 1.9±0.3 to 0.4±0.1 mg/day and decreased morphine sulfate use from 5.5±1.3 to 0.4±0.2 mg/day (P<0.001 for all). Complete response, defined as no rest angina, was achieved in 25 patients, while 8 patients experienced greater than a 50% reduction in episodes and 2 patients where nonresponders. Secondary: Not reported
Karlberg et al[45] NTG IV titrated from 1.5 mL/hour in <1 hour to a maximum of 12 mL/hour vs placebo	DB, PC, RCT Patients with recent onset of chest pain, suggestive of myocardial ischemia or worsening of previously stable angina pectoris and clinical evidence of underlying coronary artery disease	N=143 48 hours	Primary: Reduction in ongoing signs of myocardial ischemia [more than 2 angina attacks responding to 1-3 sublingual NTG tablets and lasting <20 minutes (AP1), or 1 angina attack lasting >20 minutes, despite 3 sublingual NTG tablets (AP2)], leukocyte activation, inhibition of platelet aggregation Secondary: Adverse effects	Primary: Treatment with NTG IV resulted in fewer patients (13) experiencing ongoing signs of ischemia (AP1 + AP2) than placebo (25; P<0.03). There were significantly less patients on active treatment that required >2 sublingual NTG tablets compared to placebo (12 vs 22; P<0.005). There was no significant difference found between groups in regards to leukocyte activation or inhibition of platelet aggregation. Secondary: Active treatment was stopped in 7 patients compared to 0 in the placebo group (P<0.001). Five patients terminated therapy prematurely because of headache while 2 patients stopped because of a decrease in blood pressure and bradycardia.
Heart Failure				
Cohn et al[46] V-HeFT I	AC, DB, PC, RCT	N=642 3 years	Primary: Mortality	Primary: There was a 34% risk reduction in mortality by 2 years in the ISDN plus hydralazine group compared to placebo (P<0.028). Cumulative mortality rates

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
ISDN 160 mg daily plus hydralazine 300 mg daily vs prazosin 20 mg daily vs placebo	Men with impaired cardiac function and reduced exercise tolerance on digoxin and a diuretic		Secondary: Effect on left ventricular function	of 25.6% and 36.2% were observed in the ISDN plus hydralazine group at 2 and 3 years respectively, compared to 34.3% and 46.9% in the placebo group (*P* value not reported). The results found in the prazosin group were similar to placebo. Secondary: A significant increase in the left ventricular ejection fraction was reported at 8 weeks and 1 year in the ISDN plus hydralazine treatment group, but not in either the prazosin or placebo groups.
Cohn et al[47] ISDN 40 mg QID and hydralazine 75 mg QID (individual agents, concurrent therapy) vs enalapril 10 mg BID	AC, DB, RCT Men with heart failure (primarily NYHA class II and III), receiving digoxin and diuretics	N=804 2 years	Primary: All-cause mortality Secondary: Not reported	Primary: The results demonstrated significantly lower mortality after 2 years with enalapril (18%) vs ISDN and hydralazine (25%; *P*=0.016). In addition, overall mortality tended to be lower with enalapril vs ISDN and hydralazine (*P*=0.08). Secondary: Not reported
Taylor et al[48] A-HeFT ISDN 20 mg plus hydralazine 37.5 mg TID increased to ISDN 40 mg plus hydralazine 75 mg TID vs placebo	DB, MC, PC, RCT Patients ≥18 years of age, self-identified as of African descent, with NYHA class III or IV heart failure on stan-dard therapy for at least 3 months	N=1,050 Mean duration of follow-up was 10 months	Primary: A composite score made up of weighted values for death from any cause, a first hospitalization for heart failure, quality of life changes Secondary: Individual components of the primary composite score	Primary: Combination of vasodilators in addition to standard therapy had significant mortality benefit (mortality rate of 6.2% vs 10.2%; *P*=0.02). From a range of possible scores of –6 to +2, patients in the active treatment group achieved a significantly better score of –0.1±1.9 compared to –0.5±2.0 in the placebo group (*P*=0.01). Each separate value of the composite score was also significantly better in the active group when compared to placebo. There was a 43% decrease in the rate of death from any cause (HR, 0.57; *P*=0.01), and a 33% reduction in the rate of first hospitalizations (*P*=0.001). This led to the early termination of the trial. Additionally, there was a significant improvement in quality of life scores found

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	and evidence of left ventricular dysfunction within the prior 6 months			with ISDN plus hydralazine when compared to placebo (–5.6±20.6 vs –2.7±21.2; *P*=0.02). Secondary: Results of individual components were not reported.

Drug regimen abbreviations: BID=twice daily, IV=intravenous, QAM=every morning, QID=four times daily, TD=transdermal, TID=three times daily
Study abbreviations: AC=active-controlled, DB=double-blind, HR=hazard ratio, MC=multicenter, OL=open-label, OS=observational study, PC=placebo-controlled, PG=parallel-group, RCT=randomized controlled trial, XO=crossover
Miscellaneous abbreviations; A-HeFT=African-American Heart Failure Trial, ER=extended release, ISDN=isosorbide dinitrate, ISMN=isosorbide mononitrate, NTG=nitroglycerin, NYHA=New York Heart Association, V-HeFT=Vasodilator Heart Failure Trial

IX. Conclusions

Nitrates and nitrites are indicated for the acute, prophylactic and chronic treatment of angina pectoris due to coronary artery disease. Intravenous nitroglycerin is additionally FDA-approved for the control of congestive heart failure in the setting of myocardial infarction, induction of intraoperative hypotension, treatment of angina pectoris in patients who have not responded to sublingual nitroglycerin and β-blockers and treatment of peri-operative hypertension. Since all nitrates have the same pharmacologic effects, product selection is based on desired onset and duration of action. Nitroglycerin sublingual tablets have long demonstrated their utility as a treatment for acute angina due to their rapid onset of action. The nitroglycerin sublingual spray possesses no known clinical advantage over the sublingual tablets. Nitroglycerin, when administered buccally every 4 hours, has shown similar efficacy to intravenous administration over a 24-hour period in patients with unstable angina.[43] Both isosorbide mononitrate and isosorbide dinitrate are available generically. Furthermore, nitroglycerin extended-release capsules, injection, ointment, sublingual tablets, and transdermal patches are all available generically.

The phosphodiesterase inhibitors, used for erectile dysfunction, are contraindicated in all patients on nitrite or nitrate therapy. The potential for tolerance, and therefore loss of pharmacologic effect, is common to all nitrate formulations. Nitrate tolerance is minimized by ensuring a nitrate-free period and/or use of the lowest effective dose. Transient headache is an adverse effect most often associated with nitrites and nitrates. Amyl nitrite use has fallen out of favor most likely due to its high incidence of headache and other cardiovascular adverse effects as well as its potential for abuse.

The beneficial effects of nitrates for the management of chronic stable angina are evident although there is no known advantage over β-blockers or calcium channel blockers. Tolerance further limits the chronic use of this class of medications and as a result, they are considered second-line to β-blockers for chronic stable angina.[3-5,9] Isosorbide mononitrate has demonstrated statistically significant improvement in exercise duration over placebo in patients with stable angina.[37-39] Isosorbide dinitrate in combination with hydralazine has shown a 34% reduction in mortality in patients with heart failure compared to placebo (P<0.028).[46] More specifically in African American patients, this combination of vasodilators produced a lower mortality rate of 6.2% vs 10.2% for placebo.[48] The efficacy of isosorbide dinitrate and hydralazine is further recognized in clinical practice guidelines for the management of congestive heart failure.[13-17] The efficacy of intravenous nitroglycerin has been demonstrated in patients with angina unresponsive to standard therapy with a reduction in angina episodes, doses of sublingual nitroglycerin and morphine sulfate (P<0.001).[41] Furthermore, sublingual and intravenous nitroglycerin are both recommended in unstable angina, myocardial infarction and acute coronary syndromes.[5-7,10,12]

X. Recommendations

Based on the information presented in the above review, no changes are recommended to the current approval criteria for the nitrates and nitrites:

Dilatrate-SR® and Imdur® require prior authorization with the following approval criteria:

- The patient has had a side effect, allergy, or treatment failure to at least two of the following medications: isosorbide dinitrate ER tablet, isosorbide mononitrate ER tablet, nitroglycerin ER capsule or Nitro-time®. If a product has an AB rated generic, one trial must be the generic formulation.

Ismo®, Isordil®, Monoket® require prior authorization with the following approval criteria:

- The patient has had a side effect, allergy, or treatment failure to at least two of the following medications: isosorbide dinitrate tablet or isosorbide mononitrate tablet. If a product has an AB rated generic, one trial must be the generic formulation.

Nitro-Dur® requires prior authorization with the following approval criteria:

- The patient has had a side effect, allergy, or treatment failure to Nitrek® or generic nitroglycerin transdermal patches.

Bidil® requires prior authorization with the following approval criteria:

- The prescriber provides a clinically valid reason why the patient cannot use isosorbide dinitrate and hydralazine as separate agents.

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